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OBSERVATIONS ON THE CUTANEOUS TUBERCULIN REACTION IN THE TUBERCULOUS.

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HYPERSENSITIVENESS to tuberculin when introduced into the body previously infected with the tubercle bacillus has been a recognized fact since Koch's first use of this bacillary extract in 1890. At first only general hypersensitiveness was recognized,

and it remained for von Pirquet, in 1907, to demonstrate local or skin hypersensitiveness. Later it was shown that the mucous surfaces, the eye, etc., also reacted in a hypersensitive way when tuberculin was locally administered, so that now it is assumed that all organs and tissues of a person once infected with the tubercle bacillus will show specific inflammatory or hypersensitive reactions when tuberculin is given locally. The nature of the phenomenon is not thoroughly understood. In a general way, however, it may be said that when the tubercle bacillus gains entrance to the body and incites a local reaction, or, in other words, induces a focus of infection, the body responds in a protective way with the formation of what in a general way may be termed "antibodies" to the poisonous products of the tubercle bacillus. The antibodies are at first circulating, or shortly become so, and are carried to all portions of the body, later to become fixed in the cells of the various tissues, and when tuberculin (antigen) is introduced locally in sufficient quantity an inflammatory reaction occurs. Under certain conditions such as the existence of an acute infection, notably measles or in the last stages of a progressive tuberculous infection, the local hypersensitive reaction fails to occur. Thus in a measure the reaction may be looked upon as an evidence of resisting power on the part of the host.

Unfortunately the greater proportion of all individuals have at one time been infected with the tubercle bacillus, so that the various tests based on this hypersensitive reaction will prove positive in the greater proportion of individuals when tuberculin in sufficient concentration is used. That a focus of infection need have existed before tuberculin will give rise to hypersensitive reactions has been denied by some, notably Much, Sata, etc. However, other observers have claimed to get no hypersensitive reactions unless a lesion has existed. These tests have all been done by the subcutaneous or intravenous injection methods and refer to general hypersensitiveness only. Hamburger, Baldwin, Poten, Roemer, Giebert, Joseph and others come to the latter conclusion. And, too, a few observers have presumably been able to demonstrate a loss of hypersensitiveness after removal of an existing focus, viz., Bahrat, Felix, Klemperer. However, some of these latter tests have been based solely on temperature reactions in guinea-pigs and are not conclusive. The general opinion, however, is that an infection must have taken place before the body in general will react in a hypersensitive manner to tuberculin. And upon this reaction are based the several tests for the existence of a previous infection with the tubercle bacillus. Whether or not the tests have a larger application and will give other information regarding the reaction on the part of the host is yet an undecided question. Lawrason Brown, in a series of 200 cases, could establish no other definite relation.

Ellerman and Erlandsen, in 1909 and 1910, published their observations with a new technic by which they were presumably able to differentiate active, inactive, and latent tuberculosis. The von Pirquet method was used and the strength of tuberculin varied in geometric progression. For instance, four punctures were made, and tuberculin in 1 per cent., 4 per cent., 16 per cent., and 64 per cent. dilutions were applied. Measurements of the papules were made after twenty-four and forty-eight hours, and the average size of the papules and the average differences in papule sizes were calculated. From these figures the hypersensitiveness was determined. This is, according to Morland, really the inverse of the lowest strength of tuberculin causing a reaction. A hypersensitiveness of 100 was said by Ellerman and Erlandsen to be the dividing point between active (100+) and inactive (100-) tuberculosis.

Erlandsen and Petersen and Mirauner published their observations in substantiation of the Ellerman Erlandsen method, and Mirauner would include in the active class all who showed a hypersensitiveness of over 50.

On the other hand, Bessaun and Schwenke think that the clinically tuberculous show no hypersensitiveness, but when it does occur it denotes a favorable prognosis. And when hypersensitiveness fails to increase it is of doubtful prognosis. Pringsheim comes to practically the same conclusion.

Hamburger, by repeating tests at intervals, comes to the conclusion that hypersensitiveness increases gradually in early cases, remains low in mild cases, may increase markedly and suddenly when the process becomes active, and disappear slowly when the disease rapidly progresses; and that when hypersensitiveness increases, the prognosis is good and may be an indication for the use of tuberculin.

Among the tests used for determining skin hypersensitiveness is that of Mendel, Mantoux, and Roux, the so-called intradermic test. In this method tuberculin is injected between the layers of the skin, and it has the advantage that a definite quantity of tuberculin can be used with the assurance that it is all absorbed. Thus it affords an excellent method for determining more closely the amount of tuberculin necessary to cause a local reaction. Pringsheim, Jeaneret, Holmes and others worked with the intracutaneous test. Pringsheim used fresh solutions, 1 to 100, 1 to 1000, and 1 to 10,000, and gave the tests eight days apart. In his conclusions he mentions that 10 per cent. of the von Pirquet tests done simultaneously failed to react parallel to the intracutaneous. He also states that 76 per cent. of clinically non-tuberculous children show hypersensitiveness. Holmes showed that activity of the focus increased hypersensitiveness locally. Rosenberg found that 100 per cent. of clinically tuberculous and 62 per cent. of non-tuberculous reacted to a dilution of 1 to 50,000, while 94 per cent.

of clinically tuberculous and 25 per cent. of non-tuberculous reacted to a dilution of 1 to 500,000, and from this he concludes that failure to react to the dilution of 1 to 500,000 would exclude clinical tuberculosis. Kogel says that a strong reaction with a high dilution indicates that healing processes are taking place. Jeaneret comes to the conclusion that the intradermic reaction is in a general way an indication to the grossness of the focus. He also believes that a strong intradermic reaction in a case showing few physical signs is a contra-indication for the use of tuberculin.

Ostenfeld and Permin, in an analysis of 56 cases of skin reactions find that the reactions bear in no definite way on the activity or extent of the disease.

And so conclusions are at variance and the truth not fully understood.

A series of intradermic tests were studied by us at the Adirondack Cottage Sanitarium in an effort to find any existing relation between the quantity of tuberculin necessary to incite a reaction of a certain size and the stage of the disease.

The intradermic reaction was chosen because it allowed more accurate dosage than any other method of skin test. The skin of the forearm was always the seat of the injection, and 1/10 c.c., the volume of solution, remained always the same. Koch's O. T. was the tuberculin invariably used, and care was taken that the injection was always between the upper layers of the skin and that the bevel of the needle could be seen through the skin. The quantity of tuberculin, however, was increased ten times at each successive injection until an erythema of an average diameter of 20 mm. or more was produced. Measurements were taken twenty-four and forty-eight hours after injection.

For convenience the dose is expressed in the form of a fraction as suggested by Dr. Lawrason Brown. The numerator specifies the number of zeros after the decimal point in the metric system, and the denominator the actual amount of tuberculin. Thus 0.0000001 c.c. would be recorded $\frac{1}{10,000,000}$ c.c.

Each patient was at first given an intradermic test with $\frac{1}{10,000,000}$ O. T. or less, and at the end of three or four days, provided a reaction of sufficient degree was not attained, this dose was increased ten times ($\frac{1}{1,000,000}$ c.c.). And if this dose failed to produce the required erythema it was again increased ten times ($\frac{1}{100,000}$ c.c.), and so on until an erythema of 20 mm. or more average diameter was produced. It was thought inadvisable to produce a greater erythema than this, inasmuch as the attempt in two instances was coincident with a slight general reaction.

The series was made up of 200 cases, including mostly incipient and moderately advanced cases (3 far advanced). And the reactions were studied in relation to (1) the stage of the disease; (2) the presence or absence of tubercle bacilli, also of rules; (3) the manner

of onset of the illness; (4) the progress of the case in the sanitarium; (5) the probable duration of the disease.

In general it may be said that those cases having both rales and bacilli showed a greater hypersensitiveness to tuberculin than those cases in which neither rales nor bacilli were present, and that the hypersensitiveness was more marked in the moderately advanced cases.

The majority of cases (84 per cent.) reacted to either $\frac{2}{3}$, $\frac{1}{3}$, or $\frac{1}{4}$, and the majority of these (34.5 per cent. of the total) reacted to $\frac{1}{3}$. Using $\frac{1}{3}$ as the dividing point and watching the direction of the increase in percentages for the different quantitative reactions, we find:

1. That there is a tendency for the moderately advanced case to react to a smaller quantity of tuberculin than the incipient, though the difference in percentage (6 per cent.) is too small to warrant any accurate conclusions.

2. That when tubercle bacilli are present in the sputum the percentage of all cases reacting to less than $\frac{1}{3}$ is 19 per cent. greater than when tubercle bacilli are absent (47 to 28). And that the difference in reaction is more noted in the incipient cases (48 to 27). Moderately advanced, 47 to 30.

3. That when rales are present on physical examination the percentage of all cases reacting to less than $\frac{1}{3}$ is 19 per cent. greater than when rales are not present (44 to 25). And that the difference in reaction is about the same for incipient and moderately advanced cases. Incipient, 42.5 to 24; moderately advanced, 40 to 22.

4. That when both rales and bacilli are present the percentage of all cases reacting to less than $\frac{1}{3}$ is 26 per cent. greater than when neither bacilli nor rales are present; and that the difference in reaction is about the same for incipient and moderately advanced cases. Incipient, 47 to 21; moderately advanced, 45 to 20.

5. That 36 per cent. of all cases react to less than $\frac{1}{3}$. That this percentage is increased most markedly when the onset has been hemoptoic (51 per cent.) or catarrhal (40 per cent.). And that the percentage is reduced when the onset has been insidious (26 per cent.), febrile (25 per cent.), and pleuritic (24 per cent.), the last three having almost the same percentage.

6. That the greater percentage reacting to weaker dilutions occurs when the onset is:

Insidious in the incipient cases (incipient 35 per cent. to moderately advanced 22 per cent.).

Catarrhal in the moderately advanced cases (moderately advanced 50 per cent. to incipient 31 per cent.).

Hemoptoic in the moderately advanced cases (moderately advanced 60 per cent. to incipient 40 per cent.).

When the onset is pleuritic the percentage of cases reacting to less than $\frac{1}{3}$ is about the same in both incipient and moderately

advanced cases. The cases with febrile onset were too few to be considered (4).

7. Considering the reaction from the standpoint of prognosis, that is, the relation of the reaction to the progress of the case while in the sanitarium, we find that:

Of the apparently arrested cases, 22 per cent. reacted to less than $\frac{3}{4}$.

Of the quiescent cases, 42 per cent. reacted to less than $\frac{3}{4}$.

Of the improved cases, 36 per cent. reacted to less than $\frac{3}{4}$.

Of the unimproved cases, 35 per cent. reacted to less than $\frac{3}{4}$.

The percentage of incipient and moderately advanced cases reacting to less than $\frac{3}{4}$ was approximately the same when the cases were apparently arrested or quiescent.

Apparently arrested (incipient 22 per cent.; moderately advanced, 23 per cent.).

Quiescent, (incipient, 45 per cent.; moderately advanced, 40 per cent.).

The incipient improved cases showed 25 per cent. fewer reacting to less than $\frac{3}{4}$ (21 per cent. to 46 per cent.), and the incipient unimproved cases showed 11 per cent. more reacting to less than $\frac{3}{4}$ (40 to 29 per cent.) than of the moderately advanced cases.

Considering the apparently arrested and quiescent cases as probably having passed the border-line of activity of their disease at the time of the test, and the improved and unimproved cases as being on the border-line of activity, we may possibly assume that the cases with little involvement, as they improve, lose, and as they get worse, gain, in hypersensitiveness; whereas, the case of longer standing and more advanced disease, on improving, gains, and on not improving, losses in hypersensitiveness. Of course this can only be an assumption.

When the cases are considered purely from the Turban found on physical examination, the percentages reacting to less than $\frac{3}{4}$ are approximately the same for I, II and III (36 per cent., 34 per cent. and 30 per cent.), but the curve of hypersensitiveness appears to become greater as the Turban increases, for: 34 per cent. Turban I, 23 per cent. Turban II, and 8 per cent. Turban III, react to more than $\frac{3}{4}$, the percentages reacting to $\frac{3}{4}$ increasing as the Turban increases (30 per cent., 38 per cent., 62 per cent.).

When the cases are considered from the standpoint of the duration of the present illness, we find practically no variation in percentages reacting to less than $\frac{3}{4}$, when incipient and moderately advanced cases are compared.

CONCLUSIONS. 1. The nature of the focus of infection at the time of the test influences local hypersensitiveness.

2. The quantity of tuberculin necessary to incite a local reaction of 20 mm. diameter bears no definite relation to the stage of the disease. Therefore a single skin test when positive means nothing but the existence of a previous infection.